Claims

1. A combination of at least two antibodies, characterized by the following properties:

(a) it comprises at least two different multivalent antibodies, each one having at least two specificities and being characterized by features (b) and (d) or (b) and (c) as defined below;

(b) an antigen-binding domain specific to a tumor antigen;

(c) an antigen-binding domain specific to an antigen present on human T-cells; or

(d) an antigen-binding domain specific to an antigen present on CD3-epsilon negative human effector cells.

2. The combination according to claim 1, wherein the tumor antigen is human CD19.

3. The combination according to claim 1 or 2, wherein the CD19 antigen is expressed on human B-cells.

4. The combination according to claim 1, wherein the tumor antigen is human CD30.

5. The combination according to claim 4, wherein the CD30 antigen is expressed on human Hodgkin's cells.

6. The combination according to any one of claims 1 to 5, wherein the T cell antigen is CD3, CD28 or CD5.

7. The combination according to any one of claims 1 to 6, wherein the antigen present on CD3-epsilon negative human effector cells is CD16, CD64, CD32 or NKG-2D receptor.

8. The combination according to any one of claims 1 to 7, wherein the antibodies are devoid of constant regions.

9. The combination according to any one of claims 1 to 8, wherein at least two antibodies are multimeric antibodies.

10. The combination according to any one of claims 1 to 9, which comprises single chain Fv-antibodies comprising at least four immunoglobulin variable V_H and V_L domains, either separated by peptide linkers or by no linkers.

11. The combination according to any one of claims 1 to 9, which comprises heterodimers of two hybrid single chain Fv-antibodies, each consisting of V_H and V_L domains of different specificity against a tumor antigen and an antigen present on CD3-epsilon negative human effector cells or an antigen present on human T cells, either separated by peptide linkers or by no linkers.

12. The combination according to any one of claims 1 to 9, which comprises homodimers of single chain Fv-antibodies comprising at least four V_H and V_L domains of different specificity against a tumor antigen and an antigen present on CD3-epsilon negative human effector cells or an antigen present on human T cells, either separated by peptide linkers or by no linkers.

13. The combination of any one of claims 1 to 12, wherein said antigen-binding domains mimic or correspond to V_H and V_L regions from a natural antibody.

14. The combination according to claim 13, wherein said natural antibody is a monoclonal antibody, synthetic antibody, or humanized antibody.

15. The combination according to any one of claims 1 to 14, wherein at least one antibody is linked to an effector molecule having a conformation suitable for biological

activity or selective binding to a solid support, a biologically active substance, a chemical agent, a peptide, a protein or a drug.

16. The combination according to any one of claims 1 to 15, comprising a third antibody having an antigen-binding domain as defined in claim 1(c) or (d) which is different from the antigen-binding domains of the first and second antibody.

17. The combination of any one of claims 1 to 15, comprising a first antibody which is a multivalent multimeric antibody specific to CD19 and CD16, a second antibody which is a multivalent multimeric antibody specific to CD19 and CD3, and, optionally, a third antibody which is specific to CD28.

18. Polynucleotides, which encode the antibodies of the combination according to any one of claims 1 to 17.

19. An expression vector comprising the polynucleotides of claim 18.

20. A host cell containing the expression vector of claim 19.

21. A process for the preparation of a combination of antibodies according to any one of claims 9 to 17, wherein (a) DNA sequences encoding the peptide linkers are ligated with the DNA sequences encoding the variable domains such that the peptide linkers connect the variable domains resulting in the formation of a DNA sequence encoding a monomer of a multivalent multimeric antibody, (b) the DNA sequences encoding the various monomers are expressed in a suitable expression system, and (c) the antibodies are combined.

22. A composition containing the combination of antibodies according to any one of claims 1 to 17, the polynucleotides of claim 18 or the expression vector of claim 19.

23 The composition of claim 22, which is a pharmaceutical composition optionally further comprising a pharmaceutically acceptable carrier or a diagnostic composition optionally further comprising suitable means for detection.

24. Use of the combination of antibodies of any of claims 1 to 17, the polynucleotides of claim 18 or the expression vector of claim 19 for the preparation of a pharmaceutical composition for treatment of B-cell malignancies, B-cell mediated autoimmune diseases or the depletion of B-cells.

25. Use according to claim 24, wherein said B-cell malignancy is non-Hodgkin's lymphoma.

26 Use of the combination of antibodies of any of claims 1 to 17, the polynucleotides of claim 18 or the expression vector of claim 19 for the preparation of a pharmaceutical composition for treatment of Hodgkin's disease.

27 Use of the polynucleotides of claim 18 or the expression vector of claim 19 for the preparation of a composition for gene therapy.